c. synthesizing vaccine oligopeptide, wherein the vaccine oligopeptide having amino acid sequences corresponding to the amino acid sequences of the signal oligopeptide of maximum electrical charge.

11. (Amended) A method of producing a therapeutic peptide as a vaccine in the prevention of human disease caused by a protein, the method comprising:

a. identifying a protein responsible for causing human disease;

b. identifying a signal oligopeptide sequence within the structure of the disease causing protein, the signal oligopeptide representing the amino acid sequences of maximum electrical charge of the protein;

c. synthesizing vaccine oligopeptide, wherein the vaccine oligopeptide having amino acid sequences corresponding to the amino acid sequences of the signal oligopeptide of maximum electrical charge; and

d. using an evolutionary comparison, wherein one or more species of animals in an evolutionary chain are selected to produce different vaccine oligopeptides to the same disease causing protein.

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REMARKS

Claims 1-11are pending and under examination. Claims 1-11 have now been amended to particularly point out and distinctly claim the subject matter of the invention. No new matter is introduced. Applicant acknowledges the Examiner's statement that the claimed invention is apparently free of the art of record.

35 U.S.C. § 112 Second Paragraph Rejections

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, second paragraph. In particular, the Examiner alleges indefiniteness for the term "one or more" in claims 1-11 and the step number in claim 11. The term "one or more" has been deleted; and the step number has been corrected. This amendment merely reflects a proper term usage without altering any claim scopes. Therefore, Applicant respectfully submits that the claim amendment does not constitute a narrowing amendment. The amendment shall overcome the 35 U.S.C. § 112 second paragraph rejections.

35 U.S.C. § 112 First Paragraph Rejections

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, for failing the written description requirement. The Examiner alleges that the specification does not reasonably convey one skilled in the art that the inventors had possession of the invention. In particular, the

Examiner alleges no written description for i) identifying a protein responsible for causing disease; ii) identifying a signal peptide; iii) the evolutionary chain method; iv) producing different immunogenic responses in humans; v) selecting the vaccine oligopeptide produced by the animal; and vi) various modifications of the oligopeptide. Applicant respectfully submits that the rejection is traversed.

The written requirement under 35 U.S.C. § 112 requires a showing that the applicant was in possession of the claimed invention at the time of filing. The standard is whether the inventor conveys with reasonable clarity to **those of skill in the art** that he was in possession of the subject matter of the claims. The compliance is essentially a fact-based inquire and will "necessarily vary depending on the nature of the invention claimed." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). In fact, the written description requirement does not require the applicant "to describe **exactly** the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (emphasis added).

Here, the present claimed invention is directed to a method of producing a vaccine from a signal oligopeptide. Independent claims recite processes for preparing such a vaccine. The specification provides detailed disclosure to allow persons of ordinary skill in the art to recognize that the inventor have in possession of the claimed invention. For instance, claim 1 requires 4 steps, one skilled in the art, after reading example 5 and amino acid sequence listings 1-360; table 1 and figures 2 and 3; and the entire specification would recognize that the inventor had possession of the claimed invention. The specification conveys to one skilled in the art concerning about identifying a signal oligopeptide sequence having maximum electrical charges (page 11, specification) and evolutionary comparison step (page 19, specification). Here, the Examiner subjectively alleges (without basis) a lack of written description and places himself as "one of ordinary skilled in the art," a situation which the Federal Circuit court has explicitly stated to be improper.

The case law is clear that "absence of working example, denominated as such, does not compel conclusion that specification does not satisfy requirements of 35 U.S.C. § 112." In re Long

(1966) 54 CCPA 835, 368 F2d 892, 151 USPQ 640. Here, the specification provides working examples, Applicant submits that the disclosure satisfies the written description requirement.

In In re Alton (1996),the Federal Circuit discussed the burden of establishing and overcoming a *prima facie* case of noncompliance with the written description requirement during PTO prosecution of a patent application. In re Alton, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996). "The examiner bears the initial burden ... of presenting a *prima facie* case of unpatentability.' ... Insofar as the written description requirement is concerned, that burden is discharged by 'presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.' *Id.* If, the specification contains a description of the claimed invention, albeit not in *ipsis verbis* (in the identical words), then the examiner, in order to meet the burden of proof, must provide reasons why one of ordinary skill in the art would not consider the description sufficient"

Hence, in the absence of an objective reason basis, Applicant respectfully submits that the Examiner fails to meet the initial *prima facie* burden. Accordingly, the Examiner's withdrawal of the rejection is earnestly solicited.

35 U.S.C. § 112 First Paragraph Rejections

The Examiner rejected claims 1-11 under 35 U.S.C. § 112, first paragraph, for failing the enablement requirement. In particular, the Examiner alleges that i) the specification is merely a hypothetical description and no specific examples are set forth; ii) how to select "signal oligopeptides" that would be useful for a vaccine; iii) how to define a particular protein that is responsible for a given pathological condition and thus would be undue burden to find such a particular protein; iv) how a oligopeptide can be used as a vaccine (what vaccine form to take and what components are required); v) if oligopeptide acts directly to treat pathological condition or induces an immune response to treat; vi) no evidence that such peptides would induce a differential response and that the response would treat the disease; and vii) what alogarithms are required to ascertain which amino acid sequence would be useful. Applicant respectfully submits that the rejection is traversed.

The present specification provides a detailed description of determining a hydrophilicity and surface probability algorithms (Table 1); Peptide Interception Therapy (PIT) (page 11); direct PIT is further exemplified in Figure 2; indirect PIT (page 17) and its example of Figure 4. Applicant submits that one skilled in the art, given the current knowledge in antibody and vaccine, would be enable to make and use the present invention. Specifically, one skilled artisan has been shown how i) to prepare a synthetic peptide based on the current understanding of a disease-causing protein (e.g., gp160 of HIV envelop protein in AIDS and glucagon hormone in diabetes); ii) to determine the area of maximum hydrophilicity and/or charges; iii) to prepare a vaccine or antibody. As such, the application is fully enable the full scope of the claims.

The specification further provides protein signal sequences (SED. Ids 1-360) to enable one skilled in the art to identify a disease-causing protein and to identify a signal peptide based on maximum hydrophilicity and/or electrical charges. These proteins have been attributed to many human diseases. Example 6 further illustrates the use of signal peptides in lowering cholesterol in cells.

The proper standard for determining whether the specification meets the enablement requirement was set forth in the Supreme Court decision of Mineral Separation v. Hyde, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? In In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed.Cir. 1988), the court faces an enablement issue regarding methods for producing high-affinity monoclonal antibodies against *hepatitis B surface antigen* (HbsAg). The specification teaches a procedure for immunizing mice aginst HbsAg, and the use of lymphocytes from mice to produce hybridomas that secrete monoclonal antibodies specific for HbsAg. The method claim at issue recites two process steps which the Examiner at PTO alleged the disclosure would not enable a person skilled in the art to make and use of the invention without undue experimentation.

The hybridoma-monoclonal antibody technology was invented in the mid of 1970. Note that the Wands case was decided in 1988, at a time the monoclonal antibody technique just started to become popular. In 1988, the Wands court held that the specification was enabling with respect to

the claims at issue and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed," and "all of the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406. The Wands court explicitly concluded "[e]nablement is not precluded by the necessity for some experimentation such as routine screening, However, experimentation needed to practice the invention must not be undue experimentation. "key word is 'undue,' not 'experimentation.'" *Id.* at 1404. The Wands court discarded the PTO's position that "only 4 out of 143 hydridomas, or 2.8 percent, were proved to fall within the claims." *Id.* at 1404, and found that "the amount of effort needed to obtain such antibodies is not excessive." *Id.* at 1407.

For future guidance, the Wands Court further listed eight factors for enablement analysis:

1) The breadth of the claims;
2) The nature of the invention;
3) The state of the prior art;
4) The level of one of ordinary skill;
5) The level of predictability in the art;
6) The amount of direction provided by the inventor;
7) The existence of working example; and
8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Applicant submits that the present case shares many factual findings that are similar to that in Wands. For instance, both involve antibody technology and both recite process steps in their preparation. The present invention specifically relates to a method of producing an immunogenic response (i.e., vaccine) using a signal oligopeptide. Considering all the Wards' factors in the present case, Applicant submit: i) the specification provides detailed disclosure, ii) there is a high skill level of one of ordinary artisan at the time of patent filing, iii) there is good predictability in vaccine art; iv) the specification provides adequate directions; v) the specification provides working examples; v) and algorithm and immunization procedures are merely routine (but not undue).

35 U.S.C. § 112 is factual standard and as such requires court to consider what may be expected knowledge of person skilled in pertinent art at time invention was made; this requires court to consider constantly increasing body of technical and scientific knowledge which such person may

be expected to have; thus, standard may well be different from that applied by court in prior decision 13 years ago. In re Wilke (1963) 50 CCPA 964, 314 F2d 558, 136 USPQ 435.

The present application has a filing date of June 15, 2001, some 13 years after the Wands case. There has been a significant further advancement in knowledge and skill in one of ordinary art regarding the peptide technology, human diseases and vaccine preparation. It is illogical and irony to allege that the present specification fails the enablement requirement despite the further knowledge advancement; and yet the Wands' court in some 13 years ago has held the enabling disclosure relating to monoclonal antibody preparation at its infancy stage.

It is established patent law that so long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, the enablement requirement of 35 U.S.C. §112 is satisfied. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Furthermore, a single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled since at least that embodiment would be enabled. MPEP 2164.02. Here, we have provided working examples in i) identifying a disease-causing protein, ii) synthesizing a signal protein after determining hydrophilicity and/or charges, and iii) how to use the invention in therapeutic application (e.g., cellular cholesterol metabolism).

The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Because the present specification provides detailed instructions of how to make and use other embodiments, Applicant respectfully submits that the invention is not undue (e.g., to screen a therapeutic peptide using the present disclosure) and is fully enabled for the full scope of the claims.

For at least the foregoing reasons, Applicant respectfully submits that the ground for rejection has been negated. Accordingly, the Examiner's withdrawal of the rejection is earnestly solicited.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully submits that claims 1-11are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is urged to telephone the undersigned at (212) 908-6018. The undersigned may also be contacted by email at slo@kenyon.com.

Respectfully Submitted,

Dated: December 12, 2002 By: _____

Siu K. Lo
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MARKED-UP TO SHOW CHANGES

1. (Amended) A method of producing therapeutic peptides as vaccines in the prevention of human disease caused by a protein, the method comprising:
   a. identifying a protein responsible for causing human disease;
   b. identifying [one or more] a signal oligopeptide sequences within the structure of the disease causing protein, wherein the [one or more] signal oligopeptide[s] representing the amino acid sequence of maximum hydrophilicity of the protein; and
   c. synthesizing [one or more] a vaccine oligopeptide[s], the vaccine oligopeptide[s] having amino acid sequences corresponding to the amino acid sequences of the signal oligopeptides of maximum hydrophilicity.

2. (Amended) The method of claim 1 further comprising a method of identifying [one or more] a signal oligopeptide sequence[s] within the structure of the disease causing protein, the [one or more] signal oligopeptide[s] representing the amino acid sequence of maximum surface probability of the amino acids in the disease causing protein.

3. (Amended) The method of claim 1 further comprising a method of identifying [one or more] a signal oligopeptide sequence[s] within the structure of the disease causing protein, the [one or more] signal oligopeptide[s] representing the amino acid sequence of maximum electrical charge of the amino acids in the disease causing protein.

4. (Amended) The method of claim 1 further comprising an evolutionary comparison method, wherein [one or more] a species of animals in an evolutionary chain [are] is selected to produce a different vaccine oligopeptide[s] to the same disease causing protein.

5. (Amended) The method of claim 1 further comprising an optimization step, wherein the [one or more] vaccine oligopeptide[s are] is manipulated through [one or more] an amino acid residue substitution[s], amino acid deletion[s], or amino acid insertion[s], or any combination thereof, to produce an optimized immunogenic response in vaccinated humans.

6. (Amended) The method of claim 1 wherein the immunogenic response of the vaccine oligopeptide[s] in humans is enhanced by repetition of the vaccine oligopeptides to form a linear polypeptide.

7. (Amended) The method of claim 1 wherein the [inimunogenic] immunogenic response of the vaccine oligopeptide[s] in humans is enhanced by repetition of the vaccine oligopeptide[s] to form a cyclic polypeptide.

8. (Amended) The method of claim 1 wherein the immunogenic response of the vaccine oligopeptides in humans is enhanced by coupling of [one or more of the] a vaccine oligopeptide[s] to an immunogenic protein or non-protein haptens.

9. (Amended) The method of claim 1 wherein the area of maximum hydrophilicity is identified by [one or more] a hydrophilicity determining algorithm.

10. (Amended) A method of producing therapeutic peptides as vaccines in the prevention of human disease caused by a protein, the method comprising:

a. identifying a protein responsible for causing human disease;

b. identifying [one or more] a signal oligopeptide sequence[s] within the structure of the disease causing protein, the [one or more] signal oligopeptide[s] representing the amino acid sequences of maximum electrical charge of the protein; and

c. synthesizing [one or more] vaccine oligopeptide[s], wherein the vaccine oligopeptide[s] having amino acid sequences corresponding to the amino acid sequences of the signal oligopeptide[s] of maximum electrical charge.

11. (Amended) A method of producing a therapeutic peptide[s] as a vaccine[s] in the prevention of human disease caused by a protein, the method comprising:

[d]a. identifying a protein responsible for causing human disease;

[e]b. identifying [one or more] a signal oligopeptide sequence[s] within the structure of the disease causing protein, the [one or more] signal oligopeptide[s] representing the amino acid sequences of maximum electrical charge of the protein;

[f]c. synthesizing [one or more] vaccine oligopeptide[s], wherein the vaccine oligopeptide[s] having amino acid sequences corresponding to the amino acid sequences of the signal oligopeptide[s] of maximum electrical charge; and

[g]d. using an evolutionary comparison [step], wherein one or more species of animals in an evolutionary chain are selected to produce different vaccine oligopeptides to the same disease causing protein.